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=> s human Rhesus D antigen
L1 8 HUMAN RHESUS D ANTIGEN

=> s human Rh D antigen
L2 12 HUMAN RH D ANTIGEN

=> dup remove l2
PROCESSING COMPLETED FOR L2
L3 8 DUP REMOVE L2 (4 DUPLICATES REMOVED)

=> d l3 1-8 cbib abs

L3 ANSWER 1 OF 8 MEDLINE on STN DUPLICATE 1
2001054369 Document Number: 20394848. PubMed ID: 10938935. Site directed mutagenesis of the **human Rh D antigen**: molecular basis of D epitopes. Avent N D; Liu W; Scott M L; Jones J W; Voak D. (Department of Biological & Biomedical Sciences, University of the West of England, UK.. neil.avent@uwe.ac.uk) . VOX SANGUINIS, (2000) 78 Suppl 2 83-9. Ref: 35. Journal code: 0413606. ISSN: 0042-9007. Pub. country: Switzerland. Language: English.

AB Previous attempts to define the molecular configuration of D epitopes has been confined to the analysis of the serological profile and Rh D molecular structure of partial D phenotypes. There are numerous drawbacks in this approach, most fundamental of which is that with the exception of RoHar, partial D phenotypes are defined by the loss of D epitope expression, and is thus difficult to directly correlate a specific amino acid to a particular D epitope. Furthermore, most partial D phenotypes are associated with multiple amino acid changes in the mutant Rh protein species associated with partial D expression. In our study we have applied site directed mutagenesis to introduce RhD amino acids in a stepwise manner to a Rh cE cDNA. This cDNA was introduced into K562 cells using retroviral mediated gene delivery, and D epitope expression analysed by flow cytometry. Our study provides evidence for at least six different epitope clusters on the external face of the Rh D protein. The relative predicted positions of these epitope clusters has resulted in us presenting a model for the hypothetical arrangement of external Rh D protein loops.

L3 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
1999:103374 Document No. 130:307330 The genomic organization of the partial d category DVa: the presence of a new partial D associated with the DVa phenotype. Omi, Toshinori; Takahashi, Junko; Tsudo, Naoki; Okuda, Hiroshi; Iwamoto, Sadahiko; Tanaka, Mitunobu; Seno, Taiko; Tani, Yoshihiko; Kajii, Eiji (Department of Legal Medicine and Human Genetics, Jichi Medical School, Tochigi, 329-0498, Japan). Biochemical and Biophysical Research Communications, 254(3), 786-794 (English) 1999. CODEN: BBRCA9. ISSN: 0006-291X. Publisher: Academic Press.

AB Within the Rh blood group, the partial D phenotype is a well known RhD variant, that induces Rh-incompatible blood transfusion and hemolytic diseases in the newborn. The partial D category DVa phenotype (DVa Kou.) results from a hybrid of RhD-CE-D transcript. We demonstrated a genomic organization of the hybrid RHD-CE-D gene leading to the DVa phenotype, and

showed that the DVa genes were generated from gene conversion between the RHD and the RHCE genes in relatively small regions. This study also revealed the presence of a new partial D assocd. with the DVa phenotype, which we termed the DVa-like phenotype. In this phenotype, five RHD-specific nucleotides were replaced with the corresponding RHCE-derived nucleotides on the exon 5 of the RHD gene. In addn., two variants of the mutated RHD genes at nucleotide 697 were revealed in the RhD variant samples. These results will provide useful information for future research into the diversification of the Rh polypeptides. (c) 1999 Academic Press.

L3 ANSWER 3 OF 8 MEDLINE on STN DUPLICATE 2

1998171920 Document Number: 98171920. PubMed ID: 9510931. Stable solid-phase Rh antigen. Yared M A; Moise K J; Rodkey L S. (Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX 77030, USA.) TRANSFUSION MEDICINE, (1997 Dec) 7 (4) 311-7. Journal code: 9301182. ISSN: 0958-7578. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Numerous investigators have attempted to isolate the Rh antigens in a stable, immunologically reactive form since the discovery of the Rh system over 56 years ago. We report here a successful and reproducible approach to solubilizing and adsorbing the human Rh antigen(s) to a solid-phase matrix in an antigenically active form. Similar results were obtained with rabbit A/D/F red blood cell antigens. The antigen preparation was made by dissolution of the red blood cell membrane lipid followed by fragmentation of the residual cytoskeleton in an EDTA solution at low ionic strength. The antigenic activity of the soluble preparations was labile in standard buffers but was stable in zwitterionic buffers for extended periods of time. Further studies showed that the antigenic activity of these preparations was enhanced, as was their affinity for plastic surfaces, in the presence of acidic zwitterionic buffers. Adherence to plastic surfaces at low pH maintained antigenic reactivity and specificity for antibody was retained. The data show that this approach yields a stable form of antigenically active **human Rh D antigen** that could be used in a red blood cell-free assay for quantitative analysis of Rh D antibody and for Rh D antibody immunoadsorption and purification.

L3 ANSWER 4 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

1989:266068 Document No.: PREV198988002150; BA88:2150. QUANTITATION OF FETAL-MATERNAL HEMORRHAGE BY FLOW CYTOMETRY A SIMPLE AND ACCURATE METHOD. NANCE S J [Reprint author]; NELSON J M; ARNDT P A; LAM H-T C; GARRATTY G. RES ASSOCIATE II, AMERICAN RED CROSS BLOOD SERV, LOS ANGELES-ORANGE COUNTIES REGION, 1130 S VERMONT AVE, LOS ANGELES, CALIF 90006, USA. American Journal of Clinical Pathology, (1989) Vol. 91, No. 3, pp. 288-292.
CODEN: AJCPAI. ISSN: 0002-9173. Language: ENGLISH.

AB A simple and objective asssay was developed for the detection and quantitation of fetal-maternal hemorrhage with the use of flow cytometry. In vitro prepared control mixtures of 10%, 2%, 1%, 0.5, 0.25%, 0.125%, and 0.06% D+ RBCs in D-RBCs were tested (8-11) different times by flow cytometry and gave mean % D+ results of 11.10%, 1.90%, 0.92%, 0.45%, 0.24%, 0.11%, and 0.05%. The coefficient of variation of preparing and testing these mixtures ranged from 11.0 to 15.9% for the 10-0.125% mixtures. Thus, flow cytometry was accurate, reproducible, and sensitive. Flow cytometry was compared with Du tests, rosette tests, and acid elution. The Du test was highly variable because it was not sensitive enough to detect a significant bleed (approximately 0.6%) in some cases and too sensitive (necessitating quantitation of an insignificant bleed) in others. The rosette test was too sensitive. Acid elution and flow cytometry results did not always agree; acid elution results were approximately twice as high as flow cytometry. The authors believe flow cytometric detection of D+ red blood cells to be more accurate than the detection of fetal hemoglobin by acid elution techniques, which is known to have poor reproducibility. Postpartum samples from 56 D- women who

delivered D+ babies were tested. Fifty-two had fetal bleeds less than 0.3% by acid elution and flow cytometry; all had negative Du test results, but there were two false positive results with the use of the rosette technique. Four had significant bleeds (.gtoreq. 0.6%); in all four cases the flow cytometry results were lower than the acid elution results. The authors were able to quantitate a bleed of fetal RBCs, which were D+ only by the Du test, in a D- mother with the use of flow cytometry, and D+ RBCs in a mother whose RBCs were of the rare DVI mosaic phenotype. This would not have been possible with the use of the standard Du or rosette techniques.

L3 ANSWER 5 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
1986:280392 Document No.: PREV198682024255; BA82:24255. FROZEN RECOVERED RED CELL BOOSTING OF FEMALE DONORS FOR ANTI-D-PRODUCTION. GABRA G S [Reprint author]; BLACK M; MITCHELL R. GLASGOW WEST SCOTLAND, BLOOD TRANSFUSION SERV, LAW HOSP, CARLUKE ML8 5ES, SCOTLAND, UK. Vox Sanguinis, (1986) Vol. 50, No. 3, pp. 137-140.
CODEN: VOSAAD. ISSN: 0042-9007. Language: ENGLISH.

AB A selected group of women previously immunized in pregnancy by the Rh(D) antigen were boosted with 0.5 ml of Rh(D)-positive frozen recovered red cells from an accredited donor panel. The response was prompt and sustained and increased the anti-D content by almost 10-fold. In spite of the reduced rate of clinical immunisation to the Rh(D) antigen, it was possible to recruit females with anti-D, acquired in pregnancy, for secondary boosting and a programme is recommended which maximizes efficiency and safety.

L3 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
1985:486426 Document No. 103:86426 Human monoclonal antibody against Rh(D) antigen and its uses. Kaplan, Henry S.; Teng, Nelson H.; Bron, Dominique G. (Leland Stanford Junior University, USA). PCT Int. Appl. WO 8502413 A1 19850606, 13 pp. DESIGNATED STATES: W: JP; RW: CH, DE, FR, GB, NL. (English). CODEN: PIXXD2. APPLICATION: WO 1984-US1939 19841126. PRIORITY: US 1983-555858 19831128.

AB A procedure is reported for obtaining monoclonal antibodies to **human Rh(D) antigen** by the hybridoma technique. This procedure has the advantage of not needing a human donor for the antibodies, as has been done in the past. Thus, B lymphocytes from an Rh- female, 2 wk after delivery of an Rh+ baby, were cultured, then fused with SHM-D33 human mouse heteromyeloma cells. After selection of appropriate clones, monoclonal antibodies were obtained which were specific for Rh(D) antigen. The hybridomas are stable over long periods of time and, since they are human, produce antibodies which can be used to isoimmunize Rh- women.

L3 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS on STN
1984:137116 Document No. 100:137116 Neoantigens appear in human IgG upon antigen binding: detection by antibodies that react specifically with antigen-bound IgG. Brown, Eric J.; Bekisz, Joseph (Lab. Clin. Invest., Natl. Inst. Allergy Infect. Dis., Bethesda, MD, 20205, USA). Journal of Immunology, 132(3), 1346-52 (English) 1984. CODEN: JOIMA3. ISSN: 0022-1767.

AB Rabbit antibodies that specifically recognized antigen-bound but not monomeric human IgG were raised. These rabbit IgG antibodies (RAb) were induced in rabbits that were made tolerant to monomeric human IgG. They bound to immune complexes (IC) made with human IgG and various antigens including tetanus toxoid, sheep erythrocytes (E), rabbit E, or **human Rh(D) antigen** + E, and were very poorly inhibited with monomeric IgG as compared to conventional rabbit anti-human IgG. RAb did not recognize complement components bound to the IgG contg. IC. Cleavage of the Fc domain from human IgG markedly decreased binding to RAb to IC. Surprisingly, RAb did not bind to heat-aggregated human IgG (agg-IgG) better than to monomeric IgG. Thus, human IgG expresses an Fc neoantigen when it binds its own antigen, and this determinant is not expressed by agg-IgG.

L3 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
1979:193614 Document No.: PREV197967073614; BA67:73614. NEAREST NEIGHBOR ANALYSES ON THE DISTRIBUTION OF RH ANTIGENS ON ERYTHROCYTE MEMBRANES. JAMES N T [Reprint author]; JAMES V. DEP HUM BIOL ANAT, UNIV SHEFFIELD, SHEFFIELD S10 2TN, YORKS, ENGL, UK. British Journal of Haematology, (1978) Vol. 40, No. 4, pp. 657-660.
CODEN: BJHEAL. ISSN: 0007-1048. Language: ENGLISH.
AB Distribution patterns of **human Rh D antigens** on erythrocyte membranes are investigated in both homozygous and heterozygous individuals using a computerized nearest neighbor analysis scheme. Analytical data is obtained from EM ferritin labeled antigenic sites. Rh D antigens occur in hyperdisperse patterns in both genotypes under speculative influence of a spectrin-like protein forming a filamentous network.

=> s weak D phenotype
L4 85 WEAK D PHENOTYPE

=> s l4 and missense mutation
L5 1 L4 AND MISSENSE MUTATION

=> d l5 cbib abs

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
1999:487380 Document No. 131:115307 **Missense mutations** and gene conversion correlated with the Rhesus **weak D phenotype**. Flegel, Willy A.; Wagner, Franz F. (DRK Blutspendedienst Baden-Wuerttemberg G.m.b.H., Germany). PCT Int. Appl. WO 9937763 A2 19990729, 64 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP8319 19981218. PRIORITY: EP 1998-101203 19980123.
AB The present invention relates to novel nucleic acid mols. encoding a Rhesus D antigen contributing to the **weak D phenotype** which are characterized by one or a combination of **missense mutations** or by a gene conversion involving exons 6-9 of the RHD and RHCE genes. The present invention further relates to vectors comprising the nucleic acid mols. of the invention, to hosts transformed with said vectors, to proteins encoded by said nucleic acid mols. and to methods of producing such polypeptides. The fact that **missense mutations** and the conversion referred to above can be directly correlated to the **weak D phenotype** has a significant impact on the routine testing of blood samples. For example, oligonucleotides and antibodies can now be designed that generally allow the detection of **weak D phenotypes** in a sample. Such oligonucleotides, antibodies as well as a variety of diagnostic methods all fall within the scope of the present invention. RhD antigens encoded by the novel nucleic acid mols. may be used for the characterization, standardization and quality control of monoclonal and polyclonal anti-D antisera. Finally, the invention relates to a kit useful for testing for the presence of **weak D phenotypes**.

=> s l4 and point mutation
L6 16 L4 AND POINT MUTATION

=> dup remove l6

PROCESSING COMPLETED FOR L6
L7 4 DUP REMOVE L6 (12 DUPLICATES REMOVED)

=> d l7 1-4 cbib abs

L7 ANSWER 1 OF 4 MEDLINE on STN
2001224159 Document Number: 21068631. PubMed ID: 11155084. RHD gene mutations and the **weak D phenotype**: an Australian blood donor study. Cowley N M; Saul A; Hyland C A. VOX SANGUINIS, (2000) 79 (4) 251-2. Journal code: 0413606. ISSN: 0042-9007. Pub. country: Switzerland. Language: English.

L7 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 1
2000450685 Document Number: 20458679. PubMed ID: 11005669. Weak D and partial D in Slovenian population through serology and genotyping. Rupreht R R; Pretnar Hartman K; Galvani V; Rozman P; Curin Serbec V. (Blood Transfusion Centre of Slovenia, Ljubljana.. rrupreht@mf.uni-lj.si) . PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, (2000) 440 (5 Suppl) R195-6. Journal code: 0154720. ISSN: 0031-6768. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB Weak D red cell phenotype (formerly D(II)) exhibits weaker serological reaction with anti-D antibodies. Weak D occurs in 0.2% to 1% of whites and is caused by qualitatively altered RhD proteins called partial D or normal, only weakly expressed RhD proteins that are called weak D. Partial D genes are hybrid alleles between RHD an RHCE genes. 23 partial RHD alleles are described. **Weak D phenotypes** with reduced expression are likely to possess the normal RHD gene, but the latest findings indicate that weak D alleles carry at least one **point mutation**. The aim of the present work was to answer an important question how to approach partial and weak D identification in diagnostic use and if it is possible to distinguish between partial D and weak D using commercially available anti-D reagents for routine use. We also wanted to evaluate D-screen kit for partial D identification. We compared phenotypes identified by serological testing and genotypes identified by RHD Multiplex PCR and D(VII) specific ASPA PCR. Our results showed that it is not possible to distinguish between partial and weak D using commercially available anti-D reagents for routine use. D-screen proved to be useful for D(VI) and D(VII) identification, whereas for partial D(DFR) identification we must look for another set of monoclonal antibodies or simply use genotyping methods. In 44 samples with not interpretable serological results out of 80 we found all RHD specific exons present and we classified the samples as weak D. Fourteen types of weak D with at least one **point mutation** were recently proposed. Designing of allele specific PCRs for identification of proposed types of weak D is in progress.

L7 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 2
1998297211 Document Number: 98297211. PubMed ID: 9633555. RHD genotyping in **weak D phenotypes** by multiple polymerase chain reactions. Legler T J; Maas J H; Blaschke V; Malekan M; Ohto H; Lynen R; Bustami N; Schwartz D W; Mayr W R; Kohler M; Panzer S. (Department of Transfusion Medicine, University of Gottingen, Germany.) TRANSFUSION, (1998 May) 38 (5) 434-40. Journal code: 0417360. ISSN: 0041-1132. Pub. country: United States. Language: English.
AB BACKGROUND: **Weak D phenotypes** involve a quantitative variation of D. The genomic basis in weak D has been disputed, however. STUDY DESIGN AND METHODS: Five sequence-specific polymerase chain reactions (SSP-PCRs) on exons 2, 5, and 7 of the RHD gene were evaluated in 248 white and 98 Japanese blood donors and compared with the results obtained by amplification of intron 4 and serology. All methods and SSP-PCR testing on the 3' non-coding region of the RHD gene were applied to the genotyping of 94 DNA samples derived from individuals expressing **weak D phenotypes**. RESULTS: Concordant results were obtained with all genotyping and phenotyping methods in testing 201 D-positive and 145 D-negative donors. Four of 94

weak D samples were typed as D-negative by amplification of intron 4 and SSP-PCR on exon 5. Phenotyping with monoclonal antibodies revealed a DVI category in one of these cases and DFR phenotype in three of these cases. One weak D sample, which reacted like normal D-positive cells with all applied monoclonal antibodies, was typed falsely negative by SSP-PCR on exon 5 because of a **point mutation** at nucleotide 667 (T-->G) that resulted in a Phe223Val amino acid substitution. In this individual, heterozygosity was found at two other amino acid positions (Glu233Gln and Val238Met) by restriction fragment length polymorphism analysis. CONCLUSION: Genetic diversity in **weak D phenotypes** is rare. Only 1 of 90 true **weak D phenotypes** (1.1%) had a genetic variation in testing on seven gene regions of the RHD gene.

L7 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 3

97234704 Document Number: 97234704. PubMed ID: 9116304. Evidence of genetic diversity underlying Rh D-, weak D (Du), and partial D phenotypes as determined by multiplex polymerase chain reaction analysis of the RHD gene. Avent N D; Martin P G; Armstrong-Fisher S S; Liu W; Finning K M; Maddocks D; Urbaniak S J. (International Blood Group Reference Laboratory, Southmead, Bristol, UK.) BLOOD, (1997 Apr 1) 89 (7) 2568-77. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB The human blood group Rh antigens are expressed by proteins encoded by a pair of highly homologous genes located at chromosome 1p34-36. One of the genes (RHCE) encodes Rh CcEe antigens, while the other (RHD) the D antigen. **Point mutations** in the RHCE gene generate the C/c and E/e polymorphisms, while it has been shown that an RHD gene deletion can generate the D-negative phenotype. We have analyzed intron 4 of the RHCE and RHD genes and have defined the site of an RHD-specific deletion located in this intron. Using a multiplex RHD typing assay, which combines a reverse polymerase chain reaction (PCR) primer, which straddles this RHD-specific sequence, and a pair of primers located in exon 10 of the RHD gene, we have analyzed 357 different genomic DNA samples derived from individuals expressing D+, D-, weak D, and partial D phenotypes. Of these, we have noted a significant discordance with our multiplex PCR assay in the D- phenotypes dCcee and dccEe (which have been previously described) and **weak D phenotypes**. Our results suggest that in five serologically D- individuals we have identified an apparently intact RHD gene. Sequence analysis of transcripts obtained from one of these individuals (of phenotype dCCee) illustrates the presence of full-length RHD transcripts, which have a **point mutation** at nucleotide 121 (C --> T), which generates an in-frame stop codon (Gln41Stop). Thus, we describe a different molecular basis for generating the D- phenotype to the complete RHD gene deletion described previously. We also show that there are discordances with serotype and the multiplex assay in weak D and partial D phenotypes, indicating that the underlying molecular basis can be heterogeneous. Existing Rh D PCR assays assume the complete absence of the RHD gene in D- phenotypes. We describe a different molecular basis for generating the D- phenotype to the complete RHD gene deletion described previously.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 15:11:53 ON 06 NOV 2003

L1 8 S HUMAN RHESUS D ANTIGEN
L2 12 S HUMAN RH D ANTIGEN
L3 8 DUP REMOVE L2 (4 DUPLICATES REMOVED)
L4 85 S WEAK D PHENOTYPE
L5 1 S L4 AND MISSENSE MUTATION

L6 16 S L4 AND POINT MUTATION
L7 4 DUP REMOVE L6 (12 DUPLICATES REMOVED)

=> s l4 and gene conversion
L8 3 L4 AND GENE CONVERSION

=> dup remove l8
PROCESSING COMPLETED FOR L8
L9 3 DUP REMOVE L8 (0 DUPLICATES REMOVED)

=> d l9 1-3 cbib abs

L9 ANSWER 1 OF 3 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
2001:163098 The Genuine Article (R) Number: 402HL. Prenatal genotyping for the RhD blood group antigen: Considerations in developing an accurate test . Allen R W (Reprint); Ward S; Harris R. HA Chapman Inst Med Genet, 5300 E Skelly Dr, Tulsa, OK 74135 USA (Reprint); HA Chapman Inst Med Genet, Tulsa, OK 74135 USA. GENETIC TESTING (WIN 2000) Vol. 4, No. 4, pp. 377-381 . Publisher: MARY ANN LIEBERT INC PUBL. 2 MADISON AVENUE, LARCHMONT, NY 10538 USA. ISSN: 1090-6576. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Experience performing prenatal genotyping for RHD has shown that consideration must be given to developing a molecular test capable of detecting recombination/**gene conversion** events involving the RHD and RHCE genes that can lead to erroneous results. Out of 50 prenatal RHD tests performed over the past 5 years, four samples were encountered that gave false-positive results. In only one of the tests, incorrect results were issued to the physician. In the other three instances, the erroneous nature of the test results was revealed through the analysis of multiple regions of the RHD gene and, more importantly, because the mother, and sometimes the father, were tested in parallel with the fetus. In an extension of the observations obtained from the prenatal testing program, a large panel of RhD-negative blood donors were subjected to molecular analysis of the RHD gene. Of 1,183 donors screened, 187 were found to phenotype as RhD negative. Of the 187 donors confirmed RhD negative serologically, 22 (11.8%) were found to retain remnants of the RHD gene that, depending upon the characteristics of the molecular assay performed, could lead to a false-positive result in a genotyping assay. On the basis of the experience presented here, it is recommended that any molecular RHD assay include an analysis of multiple areas of the RHD gene so as to allow for the detection of recombination/**gene conversion** events between the RHD and RHCE genes. Moreover, it is strongly recommended that the mother (at a minimum) and father be subjected to molecular analysis simultaneously with the fetus to confirm that the known phenotypes of the parent(s) are consistent with their respective genotypes.

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS on STN
1999:487380 Document No. 131:115307 Missense mutations and **gene conversion** correlated with the Rhesus **weak D phenotype**. Flegel, Willy A.; Wagner, Franz F. (DRK Blutspendedienst Baden-Wuerttemberg G.m.b.H., Germany). PCT Int. Appl. WO 9937763 A2 19990729, 64 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP8319 19981218. PRIORITY: EP 1998-101203 19980123.
AB The present invention relates to novel nucleic acid mols. encoding a Rhesus D antigen contributing to the **weak D phenotype** which are characterized by one or a combination of missense mutations or by a **gene conversion** involving

exons 6-9 of the RHD and RHCE genes. The present invention further relates to vectors comprising the nucleic acid mols. of the invention, to hosts transformed with said vectors, to proteins encoded by said nucleic acid mols. and to methods of producing such polypeptides. The fact that missense mutations and the conversion referred to above can be directly correlated to the **weak D phenotype** has a significant impact on the routine testing of blood samples. For example, oligonucleotides and antibodies can now be designed that generally allow the detection of **weak D phenotypes** in a sample. Such oligonucleotides, antibodies as well as a variety of diagnostic methods all fall within the scope of the present invention. RhD antigens encoded by the novel nucleic acid mols. may be used for the characterization, standardization and quality control of monoclonal and polyclonal anti-D antisera. Finally, the invention relates to a kit useful for testing for the presence of **weak D phenotypes**.

L9 ANSWER 3 OF 3 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

1999015460 EMBASE Molecular basis of **weak D phenotypes**. Wagner F.F.; Gassner C.; Muller T.H.; Schonitzer D.; Schunter F.; Flegel W.A.. Dr. W.A. Flegel, Abteilung Transfusionsmedizin, Universitatsklinikum Ulm, DRK-Blutspended. Baden-Wurttemberg, Helmholtzstrasse 10, D-89081 Ulm, Germany. war@ucsd.edu. Blood 93/1 (385-393) 1 Jan 1999.
Refs: 61.
ISSN: 0006-4971. CODEN: BLOOAW. Pub. Country: United States. Language: English. Summary Language: English.

AB A Rhesus D (RhD) red blood cell phenotype with a weak expression of the D antigen occurs in 0.2% to 1% of whites and is called weak D, formerly D(u). Red blood cells of **weak D phenotype** have a much reduced number of presumably complete D antigens that were repeatedly reported to carry the amino acid sequence of the regular RhD protein. The molecular cause of weak D was unknown. To evaluate the molecular cause of weak D, we devised a method to sequence all 10 RHD exons. Among weak D samples, we found a total of 16 different molecular weak D types plus two alleles characteristic of partial D. The amino acid substitutions of weak D types were located in intracellular and transmembraneous protein segments and clustered in four regions of the protein (amino acid positions 2 to 13, around 149, 179 to 225, and 267 to 397). Based on sequencing, polymerase chain reaction-restriction fragment length polymorphism and polymerase chain reaction using sequence-specific priming, none of 161 weak D samples investigated showed a normal RHD exon sequence. We concluded, that in contrast to the current published dogma most, if not all, **weak D phenotypes** carry altered RhD proteins, suggesting a causal relationship. Our results showed means to specifically detect and to classify weak D. The genotyping of weak D may guide Rhesus negative transfusion policy for such molecular weak D types that were prone to develop anti-D.

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=> s (flegel w?/au or wagner f?/au)
L10       4728 (FLEGEL W?/AU OR WAGNER F?/AU)

=> s l10 and weak phenotype
L11          2 L10 AND WEAK PHENOTYPE

=> s l10 and weak D phenotype
L12         27 L10 AND WEAK D PHENOTYPE

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13           9 DUP REMOVE L12 (18 DUPLICATES REMOVED)

=> d l13 1-9 cbib abs
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L13 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
2002:750033 Document No. 137:277378 Molecular biology of partial D and weak D. **Flegel, W. A.**; **Wagner, F. F.** (Abteilung Transfusionsmedizin, Universitaetsklinikum Ulm und DRK Blutspendedienst Baden-Wuerttemberg - Hessen gGmbH, Institut Ulm, Ulm, Germany). MTA Dialog, 3(8), 662-665 (German) 2002. CODEN: MDTIC4. ISSN: 1439-071X. Publisher: Hoppenstedt Bonnier Zeitschriften GmbH.

AB A review on partial and weak antigen D phenotypes caused by aberrant RHD gene. Mol. basics of the partial and **weak D phenotypes** are described. The clin. importance of detn. of both the types is discussed. Impacts on the rhesus detn. are characterized regarding serol., mol. methods, and the detn. of heterozygous fathers.

L13 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 1
2001155425 Document Number: 21108702. PubMed ID: 11161244. PCR screening for common weak D types shows different distributions in three Central European populations. Muller T H; **Wagner F F**; Trockenbacher A; Eicher N I; **Flegel W A**; Schonitzer D; Schunter F; Gassner C. (Oldenburg Institute, German Red Cross Blood Donor Service NSOB, Oldenburg, Germany.. tmueller@rdg.behringer-ingelheim.com) . TRANSFUSION, (2001 Jan) 41 (1) 45-52. Journal code: 0417360. ISSN: 0041-1132. Pub. country: United States. Language: English.

AB BACKGROUND: DNA sequencing showed RHD mutations for all **weak D phenotypes** investigated in a study from Southwestern Germany. Molecular classification of weak D offers a more reliable basis than serotyping and is relevant for optimal D transfusion strategies. STUDY DESIGN AND METHODS: Sequence-specific primers were designed to detect weak D types 1 to 5 and the partial D phenotype HMi in a modular set for conventional PCR analysis. Alternatively, all reactions were multiplexed into a single tube, and the products were identified after automated capillary electrophoresis by their size and fluorescence. **Weak D phenotype** samples from 436 donors in the Tyrol (Austria) and Northern Germany were investigated by PCR. RESULTS: More than 90 percent of the weak D types identified by PCR represented type 1, 2, or 3. The distribution among the common types varied between the Tyrol and Northern Germany ($p<0.0001$). Three new RHD alleles were identified. CONCLUSION: A PCR method of detecting the common weak D types was validated. This PCR system introduces a simple and rapid tool for routine DNA typing of weak D samples. The results confirmed that all **weak D phenotype** samples identified by current serologic criteria carry altered D proteins.

L13 ANSWER 3 OF 9 MEDLINE on STN DUPLICATE 2
2000218757 Document Number: 20218757. PubMed ID: 10753853. Weak D alleles express distinct phenotypes. **Wagner F F**; Frohmajer A; Ladewig B; Eicher N I; Lonicer C B; Muller T H; Siegel M H; **Flegel W A**. (Abteilung Transfusionsmedizin, Universitatsklinikum Ulm and DRK-Blutspendedienst Baden-Wurttemberg, Institut Ulm, Ulm, Germany.) BLOOD, (2000 Apr 15) 95 (8) 2699-708. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB The **weak D phenotype** is caused by many different RHD alleles encoding aberrant RhD proteins, raising the possibility of distinct serologic phenotypes and of anti-D immunizations in weak D. We reported 6 new RHD alleles, D category III type IV, DIM, and the weak D types 4.1, 4.2.1, 4.2.2, and 17. The immunohematologic features of 18 weak D types were examined by agglutination and flow cytometry with more than 50 monoclonal anti-D. The agglutination patterns of the partial D phenotypes DIM, D(III) type IV, and D(IV) type III correlated well with the D epitope models, those of the weak D types showed no correlation. In flow cytometry, the weak D types displayed type-specific antigen densities between 70 and 4000 RhD antigens per cell and qualitatively distinct D antigens. A Rhesus D similarity index was devised to characterize the extent of qualitative changes in aberrant D antigens and discriminated normal D from all tested partial D, including D

category III. In some rare weak D types, the extent of the alterations was comparable to that found in partial Ds that were prone to anti-D immunization. Four of 6 case reports with anti-D in weak D represented auto-anti-D. We concluded that, in contrast to previous assumptions, most weak D types, including prevalent ones, carry altered D antigens. These observations are suggestive of a clinically relevant potential for anti-D immunizations in some, but not in the prevalent weak D types, and were used to derive an improved transfusion strategy in weak D patients. (Blood. 2000;95:2699-2708)

L13 ANSWER 4 OF 9 MEDLINE on STN DUPLICATE 3
2000237983 Document Number: 20237983. PubMed ID: 10773054. Primary anti-D immunization by weak D type 2 RBCs. **Flegel W A**; Khull S R; **Wagner F F**. (Department of Transfusion Medicine, University of Ulm, Germany.. waf@ucsd.edu) . TRANSFUSION, (2000 Apr) 40 (4) 428-34. Journal code: 0417360. ISSN: 0041-1132. Pub. country: United States. Language: English.

AB BACKGROUND: D is the most immunogenic blood group antigen. In about 0.4 percent of whites, D is expressed on RBCs in a weak form. Recently, it was found that the **weak D phenotypes** are caused by a large number of distinct RHD alleles generally encoding altered D proteins. No particular molecular weak D type has yet been shown to induce anti-D. The threshold of D antigen density required for anti-D immunization is not known. CASE REPORT: A 72-year-old D- white man received apparently D- RBCs. Nineteen days later, he developed a positive DAT, and anti-D was found in his serum and an eluate from his RBCs. One donor was found to be D+ with a weak D type. The weak D type was determined by RHD exon 9-specific nucleotide sequencing from genomic DNA. The transfusion recipient showed alloanti-D. Ten months later, anti-D but no other antibody was detectable; the DAT was negative and the eluate was nonreactive. The donor of the incriminated unit was D+ (ccDEe) with weak D due to the weak D type 2 allele, expressing about 450 D antigens per RBC. CONCLUSION: This case provides formal proof that RBCs of weak D type 2 phenotype may cause alloanti-D immunization. Among the more prevalent weak D types in whites, weak D type 2 has the lowest D antigen density. Thus, units of blood from donors of the weak D type 2 phenotype should be labeled D+; the weak D type 2 phenotype may be useful for quality assurance.

L13 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS on STN
1999:487380 Document No. 131:115307 Missense mutations and gene conversion correlated with the Rhesus **weak D phenotype**.
Flegel, Willy A.; **Wagner, Franz F.** (DRK Blutspendedienst Baden-Wuerttemberg G.m.b.H., Germany). PCT Int. Appl. WO 9937763 A2 19990729, 64 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP8319 19981218. PRIORITY: EP 1998-101203 19980123.

AB The present invention relates to novel nucleic acid mols. encoding a Rhesus D antigen contributing to the **weak D phenotype** which are characterized by one or a combination of missense mutations or by a gene conversion involving exons 6-9 of the RHD and RHCE genes. The present invention further relates to vectors comprising the nucleic acid mols. of the invention, to hosts transformed with said vectors, to proteins encoded by said nucleic acid mols. and to methods of producing such polypeptides. The fact that missense mutations and the conversion referred to above can be directly correlated to the **weak D phenotype** has a significant impact on the routine testing of blood samples. For example, oligonucleotides and antibodies can now be designed that generally allow the detection of

weak D phenotypes in a sample. Such oligonucleotides, antibodies as well as a variety of diagnostic methods all fall within the scope of the present invention. RhD antigens encoded by the novel nucleic acid mols. may be used for the characterization, standardization and quality control of monoclonal and polyclonal anti-D antisera. Finally, the invention relates to a kit useful for testing for the presence of **weak D phenotypes**.

L13 ANSWER 6 OF 9 MEDLINE on STN DUPLICATE 4
1999081641 Document Number: 99081641. PubMed ID: 9864185. Molecular basis of **weak D phenotypes**. **Wagner F F**; Gassner C; Muller T H; Schonitzer D; Schunter F; **Flegel W A**. (Abteilung Transfusionsmedizin, Universitatsklinikum Ulm and DRK-Blutspendedienst Baden-Wurttemberg, Institut Ulm, Ulm, Germany.) BLOOD, (1999 Jan 1) 93 (1) 385-93. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB A Rhesus D (RhD) red blood cell phenotype with a weak expression of the D antigen occurs in 0.2% to 1% of whites and is called weak D, formerly Du. Red blood cells of **weak D phenotype** have a much reduced number of presumably complete D antigens that were repeatedly reported to carry the amino acid sequence of the regular RhD protein. The molecular cause of weak D was unknown. To evaluate the molecular cause of weak D, we devised a method to sequence all 10 RHD exons. Among weak D samples, we found a total of 16 different molecular weak D types plus two alleles characteristic of partial D. The amino acid substitutions of weak D types were located in intracellular and transmembraneous protein segments and clustered in four regions of the protein (amino acid positions 2 to 13, around 149, 179 to 225, and 267 to 397). Based on sequencing, polymerase chain reaction-restriction fragment length polymorphism and polymerase chain reaction using sequence-specific priming, none of 161 weak D samples investigated showed a normal RHD exon sequence. We concluded, that in contrast to the current published dogma most, if not all, **weak D phenotypes** carry altered RhD proteins, suggesting a causal relationship. Our results showed means to specifically detect and to classify weak D. The genotyping of weak D may guide Rhesus negative transfusion policy for such molecular weak D types that were prone to develop anti-D.

L13 ANSWER 7 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 5
1999:540653 Document No.: PREV199900540653. The **weak D phenotypes** express distinct immunohematologic features. **Flegel, W. A.** [Reprint author]; **Wagner, F. F.** [Reprint author]. DRK Ulm, Univ Ulm, Ulm, Germany. Transfusion (Bethesda), (Oct., 1999) Vol. 39, No. 10 SUPPL., pp. 80S. print.
Meeting Info.: 52nd Annual Meeting of the American Association of Blood Banks. San Francisco, California, USA. November 6-10, 1999.
CODEN: TRANAT. ISSN: 0041-1132. Language: English.

L13 ANSWER 8 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
1998:420770 Document No.: PREV199800420770. The molecular basis of weak D. **Flegel, W. A.** [Reprint author]; Gassner, C.; Mueller, T. H.; Schoenitzer, D.; Schunter, F.; **Wagner, F. F.**. Abteilung Transfusionsmedizin, Univ. Ulm, Ulm, Germany. Vox Sanguinis, (June, 1998) Vol. 74, No. SUPPL. 1, pp. 55. print.
Meeting Info.: 25th Congress of the International Society of Blood Transfusion. Oslo, Norway. June 27-July 2, 1998. International Society of Blood Transfusion.
CODEN: VOSAAD. ISSN: 0042-9007. Language: English.

L13 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 6
94353461 Document Number: 94353461. PubMed ID: 8073482. Influence of Rh phenotype on the antigen density of C, c, and D: flow cytometric study using a frozen standard red cell. **Wagner F F**. (Department of Transfusion Medicine, University of Ulm, Germany.) TRANSFUSION, (1994

Aug) 34 (8) 671-6. Journal code: 0417360. ISSN: 0041-1132. Pub. country: United States. Language: English.

AB BACKGROUND: Flow cytometry is increasingly being used for the comparison of antigen density. Indirect immune fluorescence is more sensitive than direct immune fluorescence and thus allows the study of red cells (RBCs) with a weak D antigen. STUDY DESIGN AND METHODS: In indirect immune fluorescence, when the fluorescence is standardized by the use of aliquoted frozen standard RBCs, the coefficient of variation in fluorescence intensity was less than 5 percent, which allows accurate determination of minor variations of Rh antigen density. RESULTS: For D antigen, the well-known suppressive effect of C, and the low antigen density of the **weak D phenotype**, was demonstrated. Use of epitope-specific monoclonal antibodies yielded similar results and allowed the identification of a D category IV heterozygote; the relative antigen density measured with a monoclonal antibody that reacted with D(IV) was twice that measured with a monoclonal antibody that did not react with D(IV). RBCs from C and c homozygotes had significantly more antigen than those from heterozygotes. There was significant variation in antigen density, depending on Rh phenotype: for example, D+ RBCs had less C antigen than D- RBCs, and Rh:1,2,-3,4,5 (CcDee) RBCs had more c antigen than Rh:1,2,3,4,5 (CcDEe) RBCs. There was no difference in D, C, and c antigen density in neonatal and adult RBCs. CONCLUSION: Flow cytometry is an excellent tool for the demonstration of minor differences in antigen density.

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=> s "Du phenotype"
L14         108 "DU PHENOTYPE"

=> s l14 and missense mutation
L15           1 L14 AND MISSENSE MUTATION

=> d l15 cbib abs

L15  ANSWER 1 OF 1      MEDLINE on STN
93306502  Document Number: 93306502.     PubMed ID: 8319109.    [Thirty years of
      research on congenital glucose and galactose malabsorption: from phenotype
      to genotype].    Trente ans de travaux sur la malabsorption congenitale du
      glucose et du galactose: du phenotype au genotype.
      Desjeux J F; Wright E M. (Conservatoire national des Arts et Metiers,
      Hopital Saint-Lazare, Paris. ) BULLETIN DE L ACADEMIE NATIONALE DE
      MEDECINE, (1993 Jan) 177 (1) 125-31; discussion 132-5. Journal code:
      7503383. ISSN: 0001-4079. Pub. country: France. Language: French.
AB    Intestinal absorption of glucose plays a key role in water economy as
      attested by the congenital and selective glucose and galactose
      malabsorption which is expressed as severe watery diarrhea just after
      birth, leading to life-threatening dehydration. This syndrome,
      transmitted on an autosomal recessive mode, is the consequence of a
      functional defect of the glucose-sodium cotransporter at the luminal
      membrane of the enterocyte of the small intestine. In one family, this
      defect was associated with a missense mutation at
      position 92 of the SGLT1 gene coding for the cotransporter. The mutant
      RNA reproduced the transport defect after injection in xenopus oocytes.
      These results confirm the genetic origin of the congenital defect; in
      addition they indicate that the study of the relationship between
      phenotype and genotype of congenital defects of intestinal transport may
      help in the understanding of basic intestinal functions in relation with
      human nutrition.

=> s l14 and human RhD
L16           0 L14 AND HUMAN RHD

=> s human RhD blood group
   3 FILES SEARCHED...
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L17 2 HUMAN RHD BLOOD GROUP

=> dup remove l17
PROCESSING COMPLETED FOR L17
L18 2 DUP REMOVE L17 (0 DUPLICATES REMOVED)

=> d l18 1-2 cbib abs

L18 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
2003:303949 Document No. 139:18027 Testing for the D zygosity with three different methods revealed altered Rhesus boxes and a new weak D type. Perco, Paul; Shao, Chao-Peng; Mayr, Wolfgang Richard; Panzer, Simon; Legler, Tobias Joerg (Clinical Department for Blood Group Serology, University of Vienna, Austria). Transfusion (Malden, MA, United States), 43(3), 335-339 (English) 2003. CODEN: TRANAT. ISSN: 0041-1132. Publisher: Blackwell Publishing, Inc..

AB The discrimination of D+/D+ from D+/D- partners of D- mothers with anti-D is important to est. the risk for HDN. This may be achieved if the presence or absence of the hybrid Rhesus box in the father can be demonstrated. A new PCR-SSP method specific for the hybrid Rhesus box comprising an internal amplification control was compared with two published PCR-based methods (PCR-SSP and PCR-RFLP) in 83 D+, 13 D-, and 37 weak D samples. The deletion of RHD was detectable in all D- and weak D samples. By all three methods, concordant results were obtained in 82 of 83 D+ samples, with one sample showing discrepant results. The control band in the PCR-RFLP method, specific for the downstream Rhesus box, was missing in two weak D samples, namely a weak D type 4.0 and a novel weak D type dubbed weak D type 29. Further investigations revealed an altered downstream Rhesus box in the weak D type 29 sample. In the weak D type 4.0 sample, no amplicon was achieved with any primer specific for the upstream and downstream Rhesus box. In conclusion, a PCR-SSP method with internal control was established for the detection of the hybrid Rhesus box. Polymorphisms in the downstream Rhesus box may interfere with the detection of RHD.

L18 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2003:22284 Document No.: PREV200300022284. Multiple samples with RHD-null-alleles in RHD-seronegative but RHC- or RHE-seropositive individuals. Doescher, A. [Reprint Author]; Gnoth, S. [Reprint Author]; Bauerfeind, U. [Reprint Author]; Goltz, M. [Reprint Author]; Schunter, F. [Reprint Author]; Petershofen, E. K. [Reprint Author]. Molecular Diagnostics, German Red Cross Blood Transfusion Service NSTOB, Institutes Oldenburg and Springe, Oldenburg, Germany. Vox Sanguinis, (August 2002) Vol. 83, No. Supplement 2, pp. 132. print.
Meeting Info.: 27th Congress of the International Society of Blood Transfusion held in conjunction with Canadian Society of Transfusion Medicine. Vancouver, British Colombia, Canada. August 24-29, 2002. International Society of Blood Transfusion; Canadian Society of Transfusion Medicine.
ISSN: 0042-9007 (ISSN print). Language: English.

=> s RhD
L19 3698 RHD

=> s l19 and weak
L20 181 L19 AND WEAK

=> s l20 and missense mutation
L21 6 L20 AND MISSENSE MUTATION

=> dup remove l21
PROCESSING COMPLETED FOR L21
L22 2 DUP REMOVE L21 (4 DUPLICATES REMOVED)

=> d l22 1-2 cbib abs

L22 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
2002351272 Document Number: 22065097. PubMed ID: 12070041. The DAU allele cluster of the **RHD** gene. Wagner Franz F; Ladewig Birgit; Angert Katharina S; Heymann Guido A; Eicher Nicole I; Flegel Willy A. (Abteilung Transfusionsmedizin, Universitatsklinikum Ulm and DRK Blutspendedienst Baden-Wurttemberg-Hessen, Institut Ulm, Ulm, Germany.) BLOOD, (2002 Jul 1) 100 (1) 306-11. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Variant D occurs frequently in Africans. However, considerably less **RHD** alleles have been described in this population compared with Europeans. We characterized 5 new **RHD** alleles, dubbed DAU-0 to DAU-4, that shared a T379M substitution and occurred in a cDe haplotype. DAU-1 to DAU-4 were detected in Africans with partial D phenotypes. They harbored one and 2 additional **missense mutations**, respectively, dispersed throughout the **RhD** protein. An anti-D immunization was found in DAU-3. DAU-0 carrying T379M only was detected by screening European blood donors and expressed a normal D phenotype. Within the phylogeny of the **RHD** alleles, DAU formed an independent allele cluster, separate from the DIVa, **weak** D type 4, and Eurasian D clusters. The characterization of the RH phylogeny provided a framework for future studies on RH alleles. The identification of the DAU alleles increased the number of known partial D alleles in Africans considerably. DAU alleles may be a major cause of antigen D variability and anti-D immunization in patients of African descent.

L22 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS on STN
1999:487380 Document No. 131:115307 **Missense mutations** and gene conversion correlated with the Rhesus **weak** D phenotype. Flegel, Willy A.; Wagner, Franz F. (DRK Blutspendedienst Baden-Wuerttemberg G.m.b.H., Germany). PCT Int. Appl. WO 9937763 A2 19990729, 64 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP8319 19981218. PRIORITY: EP 1998-101203 19980123.

AB The present invention relates to novel nucleic acid mols. encoding a Rhesus D antigen contributing to the **weak** D phenotype which are characterized by one or a combination of **missense mutations** or by a gene conversion involving exons 6-9 of the **RHD** and RHCE genes. The present invention further relates to vectors comprising the nucleic acid mols. of the invention, to hosts transformed with said vectors, to proteins encoded by said nucleic acid mols. and to methods of producing such polypeptides. The fact that **missense mutations** and the conversion referred to above can be directly correlated to the **weak** D phenotype has a significant impact on the routine testing of blood samples. For example, oligonucleotides and antibodies can now be designed that generally allow the detection of **weak** D phenotypes in a sample. Such oligonucleotides, antibodies as well as a variety of diagnostic methods all fall within the scope of the present invention. **RhD** antigens encoded by the novel nucleic acid mols. may be used for the characterization, standardization and quality control of monoclonal and polyclonal anti-D antisera. Finally, the invention relates to a kit useful for testing for the presence of **weak** D phenotypes.

=> d his

(FILE 'HOME' ENTERED AT 15:11:39 ON 06 NOV 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 15:11:53 ON 06 NOV 2003

L1 8 S HUMAN RHESUS D ANTIGEN
L2 12 S HUMAN RH D ANTIGEN
L3 8 DUP REMOVE L2 (4 DUPLICATES REMOVED)
L4 85 S WEAK D PHENOTYPE
L5 1 S L4 AND MISSENSE MUTATION
L6 16 S L4 AND POINT MUTATION
L7 4 DUP REMOVE L6 (12 DUPLICATES REMOVED)
L8 3 S L4 AND GENE CONVERSION
L9 3 DUP REMOVE L8 (0 DUPLICATES REMOVED)
L10 4728 S (FLEGEL W?/AU OR WAGNER F?/AU)
L11 2 S L10 AND WEAK PHENOTYPE
L12 27 S L10 AND WEAK D PHENOTYPE
L13 9 DUP REMOVE L12 (18 DUPLICATES REMOVED)
L14 108 S "DU PHENOTYPE"
L15 1 S L14 AND MISSENSE MUTATION
L16 0 S L14 AND HUMAN RHD
L17 2 S HUMAN RHD BLOOD GROUP
L18 2 DUP REMOVE L17 (0 DUPLICATES REMOVED)
L19 3698 S RHD
L20 181 S L19 AND WEAK
L21 6 S L20 AND MISSENSE MUTATION
L22 2 DUP REMOVE L21 (4 DUPLICATES REMOVED)

=> s l20 and gene conversion
L23 6 L20 AND GENE CONVERSION

=> s l23 and exons 6-9
L24 1 L23 AND EXONS 6-9

=> d l24 cbib abs

L24 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS on STN
1999:487380 Document No. 131:115307 Missense mutations and **gene conversion** correlated with the Rhesus **weak** D phenotype.
Flegel, Willy A.; Wagner, Franz F. (DRK Blutspendedienst Baden-Wuerttemberg G.m.b.H., Germany). PCT Int. Appl. WO 9937763 A2 19990729, 64 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP8319 19981218. PRIORITY: EP 1998-101203 19980123.

AB The present invention relates to novel nucleic acid mols. encoding a Rhesus D antigen contributing to the **weak** D phenotype which are characterized by one or a combination of missense mutations or by a **gene conversion** involving **exons 6-9** of the **RHD** and RHCE genes. The present invention further relates to vectors comprising the nucleic acid mols. of the invention, to hosts transformed with said vectors, to proteins encoded by said nucleic acid mols. and to methods of producing such polypeptides. The fact that missense mutations and the conversion referred to above can be directly correlated to the **weak** D phenotype has a significant impact on the routine testing of blood samples. For example, oligonucleotides and antibodies can now be designed that generally allow the detection of **weak** D phenotypes in a sample. Such oligonucleotides, antibodies as well as a variety of diagnostic methods all fall within the scope of the present invention. **RhD** antigens encoded by the novel nucleic acid mols. may be used for the characterization, standardization and quality control of monoclonal and

polyclonal anti-D antisera. Finally, the invention relates to a kit useful for testing for the presence of **weak** D phenotypes.

=> dup remove l23
PROCESSING COMPLETED FOR L23
L25 6 DUP REMOVE L23 (0 DUPLICATES REMOVED)

=> d l25 1-6 cbib abs

L25 ANSWER 1 OF 6 MEDLINE on STN
2002677511 Document Number: 22325387. PubMed ID: 11495631. **RHD** positive haplotypes in D negative Europeans. Wagner F F; Frohmajer A; Flegel W A. (Abteilung Transfusionsmedizin, Universitatsklinikum Ulm and DRK-Blutspendedienst Baden-Wurttemberg, Institut Ulm, Ulm, Germany.. franz.wagner@medizin.uni-ulm.de) . BMC Genet, (2001) 2 (1) 10. Journal code: 100966978. ISSN: 1471-2156. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: Blood group genotyping is increasingly utilized for prenatal diagnosis and after recent transfusions, but still lacks the specificity of serology. In whites, the presence of antigen D is predicted, if two or more properly selected **RHD**-specific polymorphism are detected. This prediction must fail, if an antigen D negative **RHD** positive allele is encountered. Excluding RHDpsi and CdeS frequent only in individuals of African descent, most of these alleles are unknown and the population frequency of any such allele has not been determined. METHODS: We screened 8,442 antigen D negative blood donations by **RHD** PCR-SSP. **RHD** PCR positive samples were further characterized by **RHD** exon specific PCR-SSP or sequencing. The phenotype of the identified alleles was checked and their frequencies in Germans were determined. RESULTS: We detected 50 **RHD** positive samples. Fifteen samples harbored one of three new Del alleles. Thirty samples were due to 14 different D negative alleles, only 5 of which were previously known. Nine of the 14 alleles may have been generated by **gene conversion** in cis, for which we proposed a mechanism triggered by hairpin formation of chromosomal DNA. The cumulative population frequency of the 14 D negative alleles was 1:1,500. Five samples represented a D+/- chimera, a **weak** D and three partial D, which had been missed by routine serology; two recipients transfused with blood of the D+/- chimera donor became anti-D immunized. CONCLUSION: The results of this study allowed to devise an improved **RHD** genotyping strategy, the false-positive rate of which was lower than 1:10,000. The number of characterized **RHD** positive antigen D negative and Del alleles was more than doubled and their population frequencies in Europe were defined.

L25 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
2002:433159 Document No.: PREV200200433159. **RHD** positive haplotypes in D negative Europeans. Wagner, Franz F.; Frohmajer, Alexander; Flegel, Willy A. [Reprint author]. Abteilung Transfusionsmedizin, Universitatsklinikum Ulm, Ulm, Germany. franz.wagner@medizin.uni-ulm.de; a.frohmajer@12move.de; willy.flegel@medizin.uni-ulm.de. BMC Genetics, (July 16, 2001) Vol. 2, No. 10 Cited May 17, 2002, pp. 1-15. http://www.biomedcentral.com/content/pdf/1471-2156-2-10.pdf. cited July 9, 2002. http://www.biomedcentral.com/1471-2156. online. ISSN: 1471-2156. Language: English.

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PCR-SSP. **RHD** PCR-positive samples were further characterized by **RHD** exon specific PCR-SSP or sequencing. The phenotype of the identified alleles was checked and their frequencies in Germans were determined. Results: We detected 50 **RHD** positive samples. Fifteen samples harbored one of three new Del alleles. Thirty samples were due to 14 different D negative alleles, only 5 of which were previously known. Nine of the 14 alleles may have been generated by **gene conversion** in cis, for which we proposed a mechanism triggered by hairpin formation of chromosomal DNA. The cumulative population frequency of the 14 D negative alleles was 1:1,500. Five samples represented a D+/- chimera, a **weak** D and three partial D, which had been missed by routine serology; two recipients transfused with blood of the D+/- chimera donor became anti-D immunized. Conclusion: The results of this study allowed to devise an improved **RHD** genotyping strategy, the false-positive rate of which was lower than 1:10,000. The number of characterized **RHD** positive antigen D negative and Del alleles was more than doubled and their population frequencies in Europe were defined.

L25 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS on STN
2001:813606 Document No. 137:28658 **RHD** positive haplotypes in D negative Europeans. Wagner, Franz F.; Frohmajer, Alexander; Flegel, Willey A. (Abteilung Transfusionmedizin, Universitatsklinikum Ulm and DRK-Blutspendedienst Baden-Wurttemberg, Ulm, Germany). BMC Genetics [online computer file], 2, No pp. given (English) 2001. CODEN: BGMEDS. ISSN: 1471-2156. URL: http://www.biomedcentral.com/1471-2156/2/10 Publisher: BioMed Central Ltd..

AB Blood group genotyping is increasingly utilized for prenatal diagnosis and after recent transfusions, but still lacks the specificity of serol. In whites, the presence of antigen D is predicted, if two or more properly selected **RHD**-specific polymorphisms are detected. This prediction must fail if an antigen D neg. **RHD** pos. allele is encountered. Excluding **RHD** and CdeS, frequent only in individuals of African descent, most of these alleles are unknown and the population frequency of any such allele has not been detd. We screened 8,442 antigen D neg. blood donations by **RHD** PCR-SSP. **RHD** PCR pos. samples were further characterized by **RHD** exon-specific PCR-SSP or sequencing. The phenotype of the identified alleles was checked and their frequencies in Germans were detd. We detected 50 **RHD** pos. samples. Fifteen samples harbored one of three new Del alleles. Thirty samples were due to 14 different D neg. alleles, only 5 of which were previously known. Nine of the 14 alleles may have been generated by **gene conversion** in cis, for which we proposed a mechanism triggered by hairpin formation of chromosomal DNA. The cumulative population frequency of the 14 D neg. alleles was 1:1,500. Five samples represented a D+/- chimera, a **weak** D and three partial D, which had been missed by routine serol.; two recipients transfused with blood of the D+/- chimera donor became anti-D immunized. The results of this study allowed us to devise an improved **RHD** genotyping strategy, the false-pos. rate of which was lower than 1:10,000. The no. of characterized **RHD** pos. antigen D neg. and Del alleles was more than doubled and their population frequencies in Europe were defined.

L25 ANSWER 4 OF 6 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
2001:163098 The Genuine Article (R) Number: 402HL. Prenatal genotyping for the **RhD** blood group antigen: Considerations in developing an accurate test. Allen R W (Reprint); Ward S; Harris R. HA Chapman Inst Med Genet, 5300 E Skelly Dr, Tulsa, OK 74135 USA (Reprint); HA Chapman Inst Med Genet, Tulsa, OK 74135 USA. GENETIC TESTING (WIN 2000) Vol. 4, No. 4, pp. 377-381. Publisher: MARY ANN LIEBERT INC PUBL. 2 MADISON AVENUE, LARCHMONT, NY 10538 USA. ISSN: 1090-6576. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Experience performing prenatal genotyping for **RHD** has shown

that consideration must be given to developing a molecular test capable of detecting recombination/**gene conversion** events involving the **RHD** and RHCE genes that can lead to erroneous results. Out of 50 prenatal **RHD** tests performed over the past 5 years, four samples were encountered that gave false-positive results. In only one of the tests, incorrect results were issued to the physician. In the other three instances, the erroneous nature of the test results was revealed through the analysis of multiple regions of the **RHD** gene and, more importantly, because the mother, and sometimes the father, were tested in parallel with the fetus. In an extension of the observations obtained from the prenatal testing program, a large panel of **RhD**-negative blood donors were subjected to molecular analysis of the **RHD** gene. Of 1,183 donors screened, 187 were found to phenotype as **RhD** negative. Of the 187 donors confirmed **RhD** negative serologically, 22 (11.8%) were found to retain remnants of the **RHD** gene that, depending upon the characteristics of the molecular assay performed, could lead to a false-positive result in a genotyping assay. On the basis of the experience presented here, it is recommended that any molecular **RHD** assay include an analysis of multiple areas of the **RHD** gene so as to allow for the detection of recombination/**gene conversion** events between the **RHD** and RHCE genes. Moreover, it is strongly recommended that the mother (at a minimum) and father be subjected to molecular analysis simultaneously with the fetus to confirm that the known phenotypes of the parent(s) are consistent with their respective genotypes.

L25 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS on STN

1999:487380 Document No. 131:115307 Missense mutations and **gene conversion** correlated with the Rhesus **weak** D phenotype. Flegel, Willy A.; Wagner, Franz F. (DRK Blutspendedienst Baden-Wuerttemberg G.m.b.H., Germany). PCT Int. Appl. WO 9937763 A2 19990729, 64 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-EP8319 19981218. PRIORITY: EP 1998-101203 19980123.

AB The present invention relates to novel nucleic acid mols. encoding a Rhesus D antigen contributing to the **weak** D phenotype which are characterized by one or a combination of missense mutations or by a **gene conversion** involving exons 6-9 of the **RHD** and RHCE genes. The present invention further relates to vectors comprising the nucleic acid mols. of the invention, to hosts transformed with said vectors, to proteins encoded by said nucleic acid mols. and to methods of producing such polypeptides. The fact that missense mutations and the conversion referred to above can be directly correlated to the **weak** D phenotype has a significant impact on the routine testing of blood samples. For example, oligonucleotides and antibodies can now be designed that generally allow the detection of **weak** D phenotypes in a sample. Such oligonucleotides, antibodies as well as a variety of diagnostic methods all fall within the scope of the present invention. **RhD** antigens encoded by the novel nucleic acid mols. may be used for the characterization, standardization and quality control of monoclonal and polyclonal anti-D antisera. Finally, the invention relates to a kit useful for testing for the presence of **weak** D phenotypes.

L25 ANSWER 6 OF 6 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

1999015460 EMBASE Molecular basis of **weak** D phenotypes. Wagner F.F.; Gassner C.; Muller T.H.; Schonitzer D.; Schunter F.; Flegel W.A..

Dr. W.A. Flegel, Abteilung Transfusionsmedizin, Universitatsklinikum Ulm, DRK-Blutspended. Baden-Wurttemberg, Helmholtzstrasse 10, D-89081 Ulm, Germany. war@ucsd.edu. Blood 93/1 (385-393) 1 Jan 1999.
Refs: 61.
ISSN: 0006-4971. CODEN: BLOOAW. Pub. Country: United States. Language: English. Summary Language: English.

AB A Rhesus D (**RhD**) red blood cell phenotype with a **weak** expression of the D antigen occurs in 0.2% to 1% of whites and is called **weak** D, formerly D(u). Red blood cells of **weak** D phenotype have a much reduced number of presumably complete D antigens that were repeatedly reported to carry the amino acid sequence of the regular **RhD** protein. The molecular cause of **weak** D was unknown. To evaluate the molecular cause of **weak** D, we devised a method to sequence all 10 **RHD** exons. Among **weak** D samples, we found a total of 16 different molecular **weak** D types plus two alleles characteristic of partial D. The amino acid substitutions of **weak** D types were located in intracellular and transmembraneous protein segments and clustered in four regions of the protein (amino acid positions 2 to 13, around 149, 179 to 225, and 267 to 397). Based on sequencing, polymerase chain reaction-restriction fragment length polymorphism and polymerase chain reaction using sequence-specific priming, none of 161 **weak** D samples investigated showed a normal **RHD** exon sequence. We concluded, that in contrast to the current published dogma most, if not all, **weak** D phenotypes carry altered **RhD** proteins, suggesting a causal relationship. Our results showed means to specifically detect and to classify **weak** D. The genotyping of **weak** D may guide Rhesus negative transfusion policy for such molecular **weak** D types that were prone to develop anti-D.

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Executing the logoff script...

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	151.44	151.65

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-7.81	-7.81

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